

**REMARKS**

Claims 1 and 23-59 are currently pending in the application. Applicants have amended claims 1, 23-28, 36-38, 43, 44, 48, 54 and 56 herein. Support for the amendments to claims 1, 23 and 24 can be found, for example, on page 2, lines 18-23, page 6, lines 9-12, and Figures 1, 3, 4 and 5 of the instant specification. Support for the amendments to claims 25-28 can be found, for example, in claims 1 and 23-28 as filed. Support for the amendments to claims 36-38 can be found, for example, on page 12, lines 26-28 of the instant specification. Support for the amendments to claims 43 and 44 can be found, for example, on page 10, lines 12-14 of the instant specification. Support for the amendments to claims 48, 54 and 56 can be found, for example, in claims 51 and 52 as filed. Applicants have added claims 57-59. Support for new claims 57-59 can be found, for example, on page 2, lines 18-23 of the instant application. No new matter has been added.

**Double Patenting**

The Examiner has provisionally rejected claims 1, 23, 24 and 33-35, on page 2, paragraph 4 of the Office Action, under the judicially created doctrine of double patenting over claims 1, 10, and 15 of U.S. Application No. 10/332,112.

Applicants will respond to this rejection when claims 1, 23, 24 and 33-35 have been deemed otherwise allowable, or the rejection is no longer provisional.

**Claim Objections**

The Examiner has objected to claims 25-28, on page 3, paragraph 5 of the Office Action, under 37 CFR 1.75(c) for being in improper form because a multiple dependent claim should depend from only a single claim or multiple claims in the alternative.

Applicants have amended claims 25-28 so that they no longer multiply depend. Applicants submit that claims 25-28, as amended herein, comply with 37 CFR 1.75(c), and that this objection is therefore overcome.

**Claim Rejections****35 U.S.C. § 112**

The Examiner has rejected claims 36-38, 43-44 and 51-52, on page 4, paragraph 7 of the Office Action, under 35 U.S.C. § 112, second paragraph, for indefiniteness. Specifically, the Examiner alleged that claims 36-38 are rejected for recitation of the phrase, "indication of H.

*pylori* status”, claims 43-44 are rejected for omitting the terms “anti- $\gamma$ IFN antibodies” and “anti-IL-4 antibodies” and claims 51-52 for lack of antecedent basis.

The Examiner rejected claims 36-38, on page 4, paragraph 8 of the Office Action, because the Examiner found that the phrase, “indication of *H. pylori* status,” was unclear. Applicants have amended claims 36-38 to stipulate that the status is a gastrointestinal condition status chosen from esophagus reflux, gastritis, dysplasia and gastric cancer. Here, status refers to the gastrointestinal condition status of the subject whose antibody or cytokine level is determined. The data generated for Figures 1 and 3-5 involved the independent diagnosis of *H. pylori* gastrointestinal condition status by methods known in the art, as described on page 12, lines 26-28 of the specification. Applicants submit that the meaning of “status” is clear and unambiguous in claims 36-38, as amended. Therefore, applicants request that this rejection be withdrawn.

The Examiner also rejected claims 43 and 44, on page 5, paragraph 9 of the Office Action, because the claims omitted essential elements “anti- $\gamma$ IFN antibodies” and “anti-IL-4 antibodies”. Applicants have amended claims 43 and 44 to stipulate that the  $\gamma$ IFN and IL-4 levels were measured with anti- $\gamma$ IFN and anti-IL-4 antibody assays, respectively. Applicants submit that claims 43 and 44, as amended, do not omit essential elements. Therefore, applicants request that this rejection be withdrawn.

The Examiner also rejected claims 51 and 52, on page 5, paragraph 10 of the Office Action, for incorrect antecedent basis. The Examiner alleged that claim 48, from which claims 51 and 52 depend provides antecedent basis of the detection of IgG2 antibody in the blood,  $\gamma$ IFN in the blood and IL-4 producing cells in the blood. Applicants have amended claim 48 to stipulate that the detection described is of IgG2 antibody producing cells in the blood,  $\gamma$ IFN producing cells in the blood and IL-4 producing cells in the blood. Applicants submit that claims 51 and 52 have antecedent basis from claim 48, as amended. Therefore, applicants request that this rejection be withdrawn.

**35 U.S.C. § 102**Steer

The Examiner rejected claims 1, 29, 33, 36, 39, 42 and 45, on page 6, paragraph 12 of the Office Action for being anticipated by Steer et al. Serodiagnosis and Immunotherapy 1:253-259 (1987) ("Steer"). The Examiner alleged that Steer teaches a determination of IgG2 levels, and a comparison of IgG2 with a predetermined control level.

Applicants have amended claim 1, from which claims 29, 33, 36, 39, 42 and 45 depend, to recite that the control must represent about the average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or about the average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* who are not suffering from gastric cancer. Steer does not teach this control.

The Examiner alleged in the Office Action that Table 3 on page 257 of Steer shows controls. These controls are antibody concentrations derived from patient diagnosed as normal, with gastritis, and with an ulcer. However, some of these patients were not infected with *H. pylori*. On page 256, second full paragraph Steer teaches that only 16 of 28 patients from which biopsies were taken were positive for *C. pylordis* (also known as *H. pylori*).

Further, the groups of data shown in Table 3 do not provide an average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or in subjects infected with *Helicobacter* who are not suffering from gastric cancer. The average results from patients diagnosed with gastritis or ulcer are different. Even if all of these patients were infected with *H. pylori*, (Applicants submit that they are not) these groups would not constitute controls which show the average IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or in subjects infected with *Helicobacter* who are not suffering from gastric cancer.

In order to anticipate a claim, a reference must teach every limitation of the claim. Steer does not teach every limitation of claim 1. Claims 29, 33, 36, 39, 42 and 45 depend from claim 1, and thus take on its limitations. Thus, Steer does not teach all of the limitations of claims 29, 33, 36, 39, 42 and 45. Applicants submit that Steer does not anticipate claims 1, 29, 33, 36, 39, 42 and 45 and request that this rejection be withdrawn.

Applicants have also added claim 57. Claim 57 is drawn to a method of diagnosing gastric cancer in a subject with *Helicobacter* infection and gastric cancer. Steer does not teach a subject with gastric cancer. Thus, applicants submit that Steer does not anticipate claim 57.

Stacey

The Examiner rejected claims 1, 29, 33, 36, 39, 42, 45, 48-49 and 50 on page 7, paragraph 14 of the Office Action for being anticipated by Stacey Dissertation, "Human Immune responses to *Helicobacter pylori* infection", (July 1994) ("Stacey"). The Examiner alleged that Stacey teaches a determination of IgG2 levels, and a comparison of IgG2 with a predetermined control level.

Applicants have amended claim 1, from which claims 29, 33, 36, 39, 42 and 45 depend, to recite that the control must represent about the average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or about the average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* who are not suffering from gastric cancer. Stacey does not teach this control.

The Examiner indicated that Stacey teaches various controls on pages 7-8, paragraph 15 of the Office Action. The controls that Stacey teaches are not an average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or in subjects infected with *Helicobacter* who are not suffering from gastric cancer, as claim 1, as amended, stipulates. Applicants discuss the specific controls indicated by the Examiner in Stacey below.

The controls that Stacey teaches are not an average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or in subjects infected with *Helicobacter* who are not suffering from gastric cancer. The controls that Stacey teaches on page 60, section 2.9.2 are "standard curves of absorbance against antibody subclass mass." The controls that Stacey teaches on page 29, section 1.6.1 are subjects not infected with *H. pylori*. The control that Stacey teaches on pages 78-79 is *H. pylori* negative sera. The control that Stacey teaches on pages 80, 81 and 84 is from subjects who are *H. pylori* negative.

The Examiner has also alleged that Stacey teaches controls on pages 38-71. Applicants respectfully disagree. Stacey teaches groups of subjects used in trials on pages 38-45. None of these groups, if they were to be termed "controls" represent about the average level of IgG2 anti-*H. pylori* antibody in subjects infected with *H. pylori* or about the average level of IgG2 anti-*H. pylori* antibody in subjects infected with *H. pylori* who are not suffering from gastric

cancer. The members of the groups shown on pages 38-45 of Stacey are not all or largely infected with *H. pylori*, and none were tested for average level of IgG2 anti-*H. pylori* antibody.

The Examiner further indicated additional comparisons which Stacey teaches with respect to IgG2 levels, on page 8 of the Office Action. The comparisons which Stacey makes are not those of a level of IgG2 anti-*H. pylori* antibody in an *Helicobacter* positive subject to an average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or in subjects infected with *Helicobacter* who are not suffering from gastric cancer, as claim 1, as amended, stipulates. The median IgG2 antibody levels on page 156 of Stacey are split between patients who were successfully and unsuccessfully treated with *H. pylori* eradication therapy. Figure 7.6 on page 165 of Stacey only gives the specificity of the antibodies isolated from patients at 1, 3 and 6 months after treatment for *H. pylori*.

The Examiner indicated that page 158 of Stacey recited relevant controls. Page 158 of Stacey compares antibody subtype levels of patients before and after treatment for *H. pylori*, but does not teach the comparison of a subject infected with *Helicobacter* with an average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or in subjects infected with *Helicobacter* who are not suffering from gastric cancer. At the bottom of page 158, in patients for whom the *H. pylori* treatment was unsuccessful, IgG2 levels were compared from before and after treatment. However, these levels do not represent an average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter*. The average of IgG2 anti-*H. pylori* antibody in both successfully and unsuccessfully treated *H. pylori* patients is not taught by Stacey. Thus, page 158 of Stacey does not teach the comparison of the level of IgG2 anti-*H. pylori* antibody in an *Helicobacter* positive subject to an average level of IgG2 anti-*H. pylori* antibody in subjects infected with *Helicobacter* or in subjects infected with *Helicobacter* who are not suffering from gastric cancer, as claim 1, as amended, stipulates.

Further, applicants have amended claim 48 to stipulate that the frequency of IgG2 anti-*H. pylori* antibody-producing cells must be determined. Stacey does not teach the determination of frequency of IgG2 anti-*H. pylori* antibody-producing cells.

In order to anticipate a claim, a reference must teach every limitation of the claim. Stacey does not teach every limitation of claims 1 and 48. Claims 29, 33, 36, 39, 42, and 45 depend from claim 1, and claims 50 and 51 depend from claim 48 and thus take on their respective limitations. Thus, Stacey does not teach all of the limitations of claims 29, 33, 36, 39,

42, 45, 50 and 51. Since Stacey does not anticipate claims 1, 29, 33, 36, 39, 42, 45, 48-49 and 50 this rejection should be withdrawn accordingly.

Applicants have also added claim 57. Claim 57 is drawn to a method of diagnosing gastric cancer in a subject with *Helicobacter* infection and gastric cancer. Stacey does not teach the comparison of the level of IgG2 anti-*H. pylori* antibody in a subject with gastric cancer with a predetermined control. Thus, applicants submit that Stacey does not anticipate claim 61.

Karttunen and Deltenre

The Examiner also rejected claims 23, 29, 31, 37, 40, 43, 46, 48-50, 52, and 54-55 on page 9, paragraph 16 of the Office Action for being anticipated by Karttunen *et al.* Gut 36:341-345 (1995) ("Karttunen") as evidenced by Deltenre *et al.* Acta Gastro-Enterologica Belgica 53: 193-200 (1995) ("Deltenre"). The Examiner alleged that Karttunen teaches a determination of  $\gamma$ IFN levels and a comparison of  $\gamma$ IFN levels with a predetermined control level. Deltenre demonstrates that gastric carcinoma may be a complication of *H. Pylori* related chronic gastritis.

Applicants have amended claim 23, from which claims 29, 31, 37, 40, 43 and 46, depend, to specify that the control must represent about the average level of  $\gamma$ IFN in subjects infected with *Helicobacter* or about the average level of  $\gamma$ IFN in subjects infected with *Helicobacter* who are not suffering from gastric cancer. Karttunen does not teach this control.

Karttunen teaches the comparison of  $\gamma$ IFN in patients without gastritis or *H. pylori* infection, in patients with gastritis, in patients with gastritis and *H. pylori* infection, and in patients without gastritis and with *H. pylori* infection in Figures 1 and 2 on page 344. Karttunen does not teach a control which represents about the average level of  $\gamma$ IFN in subjects infected with *Helicobacter* or about the average level of  $\gamma$ IFN in subjects infected with *Helicobacter* who are not suffering from gastric cancer, as stipulated in claim 23 as amended.

Applicants have also amended claims 48 and 54 to state that the frequency of  $\gamma$ IFN-producing cells must be determined. Claim 56 has been amended to be consistent with claim 54 from which it depends. Karttunen does not teach the determination of  $\gamma$ IFN-producing cells.

In order to anticipate a claim, a reference must teach every limitation of the claim. Karttunen does not teach every limitation of claims 23, 48 and 54. Claims 29, 31, 37, 40, 43, 46, depend from claim 1, claims 49, 50, and 52 depend from claim 48, and claim 55 depends from claim 54 and thus take on their respective limitations. Thus, Karttunen does not teach all of the limitations of claims 29, 31, 37, 40, 43, 46, 49, 50, 52, and 55. Applicants submit that Karttunen

does not anticipate claims 23, 29, 31, 37, 40, 43, 46, 48-50, 52, and 54-55 and request that this rejection be withdrawn.

Applicants have also added claim 58. Claim 58 is drawn to a method of diagnosing gastric cancer in a subject with *H. pylori* infection and gastric cancer. Karttunen does not teach the comparison of the level of  $\gamma$ IFN in a subject with gastric cancer with a predetermined control. Thus, applicants submit that Karttunen does not anticipate claim 58

Fan

The Examiner also rejected claims 24, 29, 32, 35, 38, 41, 44, 47, 48-50, 53, 54 ad 55 on page 11, paragraph 17 of the Office Action as anticipated by Fan et al. Mediators of Inflammation 4:289-292 (1995) ("Fan"). The Examiner alleged that Fan teaches a determination of IL-4 levels, and a comparison of IL-4 with a predetermined control level.

Applicants have amended claim 24, from which claims 29, 32, 35, 38, 41, 44 and 47, depend, to stipulate that the control must represent about the average level of IL-4 in subjects infected with *Helicobacter* or about the average level of IL-4 in subjects infected with *Helicobacter* who are not suffering from gastric cancer. Fan does not teach this control.

Fan teaches the comparison of IL-4 levels in *H. pylori* infected subjects to non-infected subjects in Tables 2 and 3 on page 290. Fan does not teach a control which represents about the average level of IL-4 in subjects infected with *Helicobacter* or about the average level of IL-4 in subjects infected with *Helicobacter* who are not suffering from gastric cancer, as stipulated in claim 24 as amended.

Further, applicants traverse the rejection of claims 48 and 54 as anticipated by Fan. Claims 48 and 54 stipulate that the frequency of IL-4 producing cells are determined. Fan does not teach the determination of the frequency of IL-4 producing cells. The only data shown in Fan is the actual amounts of IL-4, not the frequency of IL-4 producing cells.

In order to anticipate a claim, a reference must teach every limitation of the claim. Fan does not teach every limitation of claims 24, 48 and 54. Claims 29, 32, 35, 38, 41, 44 and 47 depend from claim 1, claims 49, 50, and 52 depend from claim 48, and claim 55 depends from claim 54 and thus take on their respective limitations. Thus, Fan does not teach all of the limitations of claims 29, 32, 35, 38, 41, 44, 47, 50, 52, and 55. Applicants submit that Fan does not anticipate claims 24, 29, 32, 35, 38, 41, 44, 47, 48-50, 53, 54 ad 55 and request that this rejection be withdrawn.

Applicants have also added claim 59. Claim 59 is drawn to a method of diagnosing gastric cancer in a subject with *H. pylori* infection and gastric cancer. Fan does not teach the comparison of the level of IL-4 a subject with gastric cancer with a predetermined control. Thus, Applicants submit that Fan does not anticipate claim 64.

### 35 U.S.C. § 103

The Examiner rejected claim 56 on page 12, paragraph 19 of the Office Action for being obvious over Fan in light of Itoh *et al.* J. Gastroenterol 34:560-570 (1999) ("Itoh"). The Examiner alleged that Fan teaches a determination of IL-4, and a comparison of IL-4 with a predetermined control level, and Itoh teaches the use of flow cytometry to detect IL-4 producing T-cells, and thus it would have been obvious to determine the level of IL-4. Applicants traverse.

As explained above, Fan does not teach the determination of the frequency of IL-4 producing cells, which was stipulated in claim 54. Itoh does not remedy the deficiency of Fan. Itoh teaches the detection of IL-4 through flow cytometry, and does not mention the correlation of IL-4 expressing cells in subjects infected with *Helicobacter* to gastric cancer.

Further, even if Fan did teach the determination of the frequency of IL-4 producing cells (Applicants assert that Fan does not teach the determination of the frequency of IL-4 producing cells) its combination with Itoh would not meet the requirements for a *prima facie* case of obviousness. Claim 54, from which claim 56 depends, and the other claims of the instant application are drawn to methods of diagnosing or predicting the risk of gastric cancer. Neither Fan nor Itoh even mention gastric cancer, let alone suggest that the comparison of IL-4 levels in subjects infected with *Helicobacter* could be used to predict or diagnose gastric cancer. Further, none of the references cited by the Examiner in the Office Action suggest the invention of claims 54 or 56, or the remaining instant claims.

Applicants submit that claim 56 is non-obvious over Fan in light of Itoh and therefore request that this rejection be withdrawn.

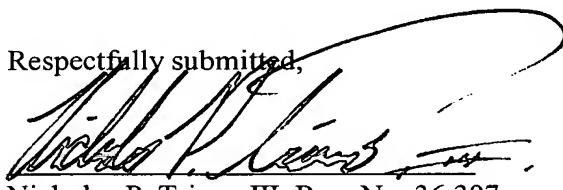
### CONCLUSION

A prompt allowance is respectfully requested. If any discussion regarding this Amendment is desired, the Examiner is respectfully urged to contact the undersigned at the

number given below, and is assured of full cooperation in progressing the application to allowance.

While applicants believe that no additional fees are needed, the USPTO is authorized to charge or credit the undersigned Deposit Account No. **50-0311**, Customer No. **30623**, Reference No. **24356-002 CON**, for any additional fees that are required.

Respectfully submitted,



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